IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Sadanobu SHIRAI et al.

Serial No. 10/524,858 Group Art Unit: 1615

Filed: February 18, 2005 Examiner: Hasan Syed Ahmed

For: PACHES CONTAINING TULOBUTEROL

DECLARATION

Honorable Commissioner of Patents

Sir:

I, Sadanobu SHIRAI, a citizen of Japan residing at 402-1, Tahishimo-machi, Takamatsu-shi, Kagawa 761-8075 Japan, declare as follows:

I graduated from Tokushima University, Department of Engineering, Faculty of Biological Science and Technology in 1992.

I was employed in TEIKOKU SEIYAKU CO., LTD. in 1992 and since then I have engaged in study of the pharmaceutical preparations.

Under my supervision, the following experiment was carried out.

1. Object

The experiment was conducted in order to confirm the difference between a patch containing 4% of turobuterol directed to the present invention and a patch containing 5% of turobuterol disclosed in Example 8 of U.S. Patent 6,117,447 which corresponds to Comparative example 6 of the present specification.

2. Test-materials

Two kinds of patches having following ingredients were tested.

Ingredients	New example Content (w/w %)	Comparative ex. 6 Content (w/w %)
Turobuterol	4	5
Oleic acid	1	0
Isopropyl myristate	0	40
Styrene·isoprene·styrene block copolymer	20	38.5
Saturated alicyclic hydrocarbon resin (Petroleum resin)	42	11
Polybutene	10	0
Polyisobutylene	0	5.5
Liquid paraffin	22	0
Dibutylhydroxytoluene	1	0
Weight of adhesive	80g/m^2	40g/m^2
Backing	PET 12μ/m^2	PET 25μ/m^2
Liner	PET 75μm (Release coating on one side)	PET 75μm (Release coating on one side)

1) New example within present claims 1 was prepared in the same manner as in the method of Example 1 of the present specification.

2) A patch of Comparative example 6 was prepared as follows. According to the above indications, styrene·isoprene·styrene block copolymer, polyisobutylene and saturated alicyclic hydrocarbon resin were mixed until being homogenous. To the mixture were added and mixed turobuterol and isopropyl myristate until being homogenous. The solution was spread on the surface of release treated PET in the amount of 40g/m^2 dried and stuck on PET backing. Thus obtained preparation was cut in a suitable size to be packed in a sealed package.

3. Test

In order to check the influence on drug-release due to the changes of preservation temperature, patches of New example and Comparative example 6 were preserved in incubator kept at 4°C and 40°C respectively for 3 weeks, and then the temperature was adjusted to room temperature.

By using the test samples, the drug permeation test on the skin extracted from rat was carried out as follows.

The skin of abdomen of a hair-cut rat was extracted and fitted on a Frantz-diffusion cell. Phosphate-buffer was used as a reservoir solution and the cell was kept to stir at 37°C during test.

A patch of New example, and a patche of Comparative examples 6 were cut in a circle having diameter 13mm (Turobuterol of New example: 4w/w%, 320μg/cm^2 and Comparative example 6: 2 w/w %, 200μg/cm^2), and the circles fitted on the extracted skin. Small amount of the reservoir solution was from time to time taken and the amount of permeated turobuterol was measured by HPLC (Drug permeation test on rat-extracted skin).

Changes of the passage with time of permeated turobuterol in case of application of patches of New example and Comparative example 6 were shown in Fig. A below.

And rates of drug permeated amount due to changes of preservation temperature on each sample are shown below.

Test example	New example	Comparative example 6
Rate of permeation	98 %*	44 %

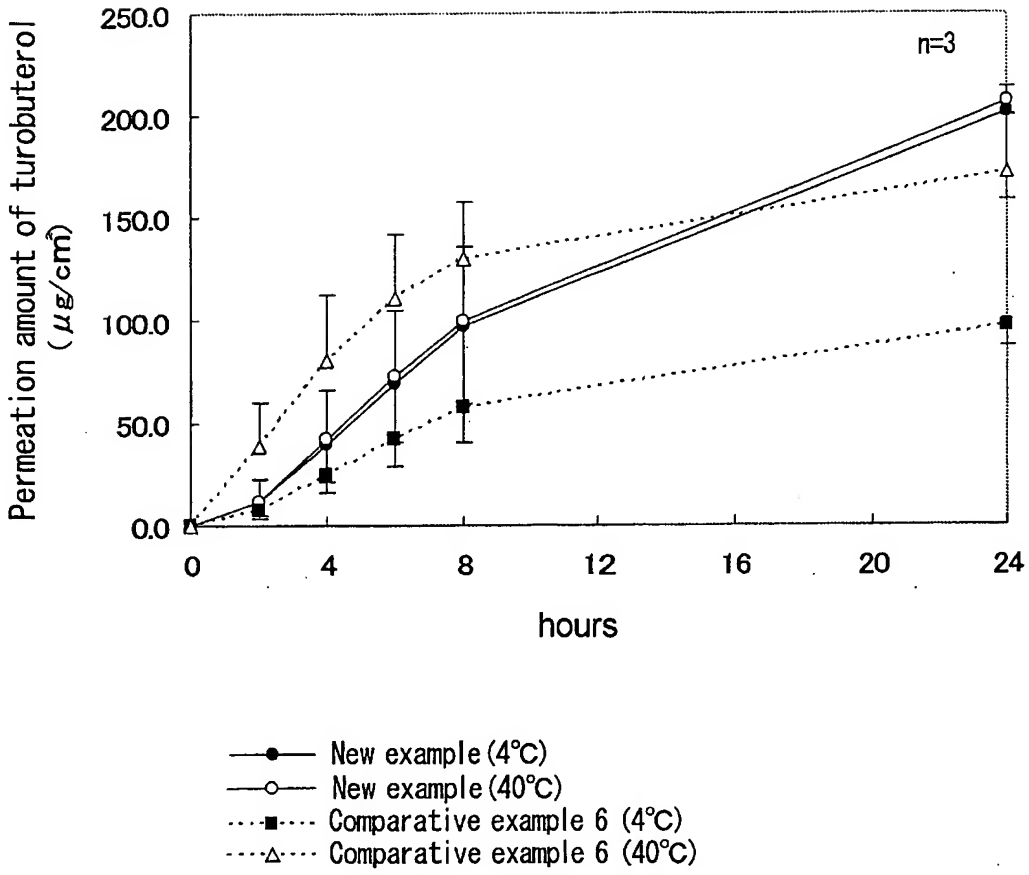
*Calculation: {permeation amount (4°C) (8 hr)} /

{permeation amount of Example 1 (40°C) (8 hr)} × 100

4. Considerarion

From this test result, the amount of permeated turobuterol in regard to the patch of New example was constant in changes of the passage with time and hardly influenced by the changes of the passage with time and by the changes of the preservation temperature. On the other hand, in regard to the patch of Comparative example 6, it showed the tendency that the amount of the permeated drug increased and the duration decreased at a latter half. The amount of the permeated drug on the patch Comparative example 6 was greatly affected by the changes of the preservation temperature.

Fig. A



The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1000 of Title 18 of the United State Code and that such willful false statement may jeopardize the validity of the above mentioned application or any patenting thereon.

This 16th day of May, 2008

Sadanobu Shirai

Sadanobu SHIRAI